Epidemiology

Bardet-Biedl syndrome (BBS) is a rare genetic disorder with severe multiorgan impairment. Its frequency in Europe and North America falls below 1:100,000 [Forsythe and Beales, 2013]. Some isolated human communities are characterized by unusually high occurrence of this disease [Sheffield, 2004]. For example, 13 BBS patients were registered among 48,000 inhabitants of the Faroe Islands, leading to disease frequency estimates of 1:3,700 [Hjortshøj et al., 2009]. BBS prevalence in Newfoundland was reported to approach 1:18,000 [Moore et al., 2005]. BBS is relatively common in the Middle East, with a frequency of 1:13,500 in some Bedouin communities and a noticeable number of families identified in several other populations [Farag and Teebi, 1989; M’hamdi et al., 2011]. Ashkenazi Jews, being apparently the most genetically studied founder community, have not yet been subjected to an exhaustive BBS epidemiologic research [Fedick et al., 2014]. It is important to comment that many of the re-
ported frequency estimates were not explicitly tailored to the DNA-based diagnosis; therefore, the available figures should be treated with caution. Up to now, only a few instances of BBS have been reported in Eastern Europe, Asia, South America, and Africa, and systematic BBS studies still remain to be done in these regions [Khan et al., 2013; Xing et al., 2014; Ece Solmaz et al., 2015; Hiran-no et al., 2015; Suspitsin et al., 2015]. There are (1) the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) at the Marshfield Clinic (https://www.marshfieldclinic.org/services/bardet-biedl-syndrome-(bbs); https://cribbs.marshfieldclinic.org/), (2) the European-based EURO-WABB registry [Farmer et al., 2013], and a number of robust international studies [Deveault et al., 2011; Ajmal et al., 2013; Fattahi et al., 2014] attempting to attract unstudied patients to BBS research.

**Clinical Manifestations**

The description of essential clinical manifestations and corresponding diagnostic criteria is largely based on a seminal study of Beales et al. [1999]. It is important to acknowledge that these diagnostic algorithms were developed before the discovery of BBS genes and based on phenotypic presentations of this syndrome [Forsythe and Beales, 2013]. The disease symptoms may significantly vary between the patients; therefore, the diagnosis relies on the number of primary and secondary features of BBS. Multiple articles summarize the data on frequencies of various symptoms in BBS patients [Beales et al., 1999; Forsythe and Beales, 2013; M’hamdi et al., 2014]. However, it is very important to realize that almost all clinical studies analyzed patients of various ages. Many individuals with BBS look virtually healthy at birth unless they were born with a polydactyly. Other symptoms of BBS tend to gradually emerge during or after the first decade of life; thus, patients diagnosed at early childhood tend to have fewer clinical features of the disease. For example, rod-cone dystrophy was reported to affect ‘only’ 93% of BBS patients; however, those who did not have eye abnormalities were younger than 8 years at the time of the study [Beales et al., 1999].

There are 6 primary features of BBS, i.e. rod-cone dystrophy, polydactyly, obesity, genital abnormalities, renal defects, and learning difficulties. Secondary features include developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus, and congenital heart disease [Forsythe and Beales, 2013]; some authors also mention hypertension, liver abnormalities, bronchial asthma, otitis, rhinitis, craniofacial dysmorphism, etc. [Baker and Beales, 2009; Forsythe and Beales, 2013; Shoemark et al., 2015; Khan et al., 2016]. It is recommended to assign BBS diagnosis to patients bearing at least 4 out of 6 primary features of the disease. If only 3 primary features are detected, 2 secondary features are required to confirm the presence of BBS. These criteria describe BBS mainly as a clinical entity; they do not fully account to the existence of patients with attenuated forms of the disease as well as to possible gene-specific manifestations of BBS [Pawlik et al., 2010; Estrada-Cuzcano et al., 2012]. It is likely that the increasing number of patients with incomplete diagnostic criteria for this syndrome will be subjected to BBS gene testing in the future, thanks to the improving availability of multigene sequencing. Furthermore, given that only polydactyly and renal abnormalities are often diagnosed at or before birth, the relaxed criteria for antenatal genetic screening are warranted [Putoux et al., 2010]. There is also a noticeable phenotypic overlap with some other ciliopathies, e.g. Alström syndrome, Joubert syndrome, Meckel syndrome, McKusick-Kaufman syndrome, or Senior-Loken syndrome, which further complicates the clinical and genetic diagnosis of BBS [Redin et al., 2012].

**BBS Genes**

The first 5 BBS loci were identified via linkage analysis of large BBS pedigrees [Kwitek-Black et al., 1993; Leppert et al., 1994; Sheffield et al., 1994; Carmi et al., 1995; Young et al., 1999] with corresponding genes cloned some years later [Mykytyn et al., 2001, 2002; Nishimura et al., 2001; Chiang et al., 2004; Fan et al., 2004; Li et al., 2004]. The first gene assigned to BBS was MKKS (MKS) already known to induce McKusick-Kaufman syndrome; given that it did not belong to previously identified BBS loci, it was named BBS6. At present, there are already 21 known BBS genes (BBS1–BBS20 and NPHP1), and their number is likely to increase due to the invention of exome sequencing and analysis of previously unstudied populations (table 1). Strikingly, all BBS genes participate in cilia functioning (fig. 1), being a part of BBSome (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, BBS17, and BBS18), chaperonin complex (BBS6, BBS10 and BBS12), basal body (BBS13, BBS14, BBS15, and BBS16) or having some related biological function (BBS3, BBS11, BBS19, BBS20, and NPHP1). These genes apparently lack redundancy, and the disruption of any of them lead to cilia impairment...
It is frequently stated that the clinical presentation of BBS does not significantly depend on the identity of genes involved; therefore, prioritization of gene testing based on phenotypic characteristics of the affected patient is not advised [Forsythe and Beales, 2013]. However, most of the available BBS patients are BBS1 and BBS10 biallelic mutation carriers, while other genetic types of the disease are described in very small patient series or even in single families. There are multiple studies emphasizing genotype-phenotype correlations, i.e. specific disease presentation in carriers of particular alleles (table 1).

It is usually stated that the analysis of known BBS genes detects biallelic mutations in \(~80\%) of BBS patients [Billingsley et al., 2011; Forsythe and Beales, 2013; Glöckle et al., 2014]. There are a number of limitations related to this issue. First, many of the identified mutations are not overtly deleterious (i.e. frameshifts, premature stop codons or alterations at splice sites), but are represented by amino acid substitutions [Muller et al., 2010; Pereiro et al., 2010; Deveault et al., 2011; Álvarez-Satta et al., 2014; Lindstrand et al., 2014]. The evaluation of the true pathogenic impact of missense mutations is highly complicated and usually relies on the segregation analysis, various bioinformatics tools and functional assays. None of these approaches is sufficiently precise, especially when only one is performed [Muller et al., 2010]. Secondly, most of the current DNA sequencing protocols have some deficiencies, i.e. they are unable to cover all potentially important regions of BBS genes [Redin et al., 2012]. Thirdly, BBS genetic studies usually do not involve MLPA or equivalent methods. For this reason, some large gene rearrangements are likely to be missed [Muller et al., 2010; Lindstrand et al., 2014]. In agreement with this, some studies report the increased occurrence of BBS gene heterozygotes among BBS patients, leaving the possibility that the mutation in the second allele remains to be overlooked due to technical limitations [Fauser et al., 2003; Hichri et al., 2005; Hjortshøj et al., 2010].

**Mode of Inheritance**

Early studies on BBS suggested the classical mode of autosomal recessive inheritance, and this model was confirmed in the initial gene discovery studies [Kwitek-Black et al., 1993; Leppert et al., 1994; Young et al., 1999]. Further research added complexity to the genetics of BBS. There are occasional observations on biallelic BBS gene mutation carriers, who remain healthy by the time of the investigation; this suggests incomplete penetrance at least for some genes and/or types of mutations [Katsanis et al., 2001; Beales et al., 2003; Estrada-Cuzcano et al., 2012]. At the same time, those patients who are affected by the disease and carry a homozygous mutation in one of the BBS genes often carry an additional heterozygous mutation in another BBS gene. These sensational observations were defined as a ‘triallelic inheritance’ and became a subject of intensive studies [Katsanis et al., 2001]. Some data sets confirm increased coincidence of homozygous and heterozygous BBS gene mutations in BBS patients, while others deny this relationship [Katsanis et al., 2002; Badano et al., 2003a; Beales et al., 2003; Fauser et al., 2003; Mykytyn et al., 2003; Hichri et al., 2005; Laurier et al., 2006; Smaoui et al., 2006; Hjortshøj et al., 2010; Abu-Safieh et al., 2012; Daniels et al., 2012; Redin et al., 2012]. Furthermore, the mechanistic basis for the pathogenic impact of heterozygous mutations remains largely elusive. The existing statistics may be compromised by the fact that the majority of available studies put both protein-truncating and presumably pathogenic missense mutations in one basket.
<table>
<thead>
<tr>
<th>Gene (synonym), chromosome localization</th>
<th>Contribution to BBS morbidity</th>
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</tr>
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<tr>
<td><strong>BBS1 (BBS2L2), 1q13</strong> [Leppert et al., 1994; Mykytyn et al., 2002; Muller et al., 2010]</td>
<td>23%</td>
<td>BBSome</td>
<td>c.1169T&gt;G (p.M390R), people of Northern European descent [Mykytyn et al., 2003]; c.1091+3G&gt;C, Faroe Islands [Hjortshøj et al., 2009]</td>
<td>Milder phenotype for BBS1 compared to BBS2 and BBS16 [Hjortshøj et al., 2010]; Better visual acuity and larger ERG amplitudes compared to patients with mutations in other BBS genes [Daniels et al., 2012]; Among patients with p.M390R mutation, homozygotes showed a relatively more severe ocular phenotype than compound heterozygotes [Castro-Sanchez et al., 2015]; Patients with missense mutations in BBS1 had a lower level of biochemical cardiovascular disease markers compared to patients with BBS10 and other BBS mutations [Fosythe et al., 2015]</td>
<td>Nonsyndromic retinitis pigmentosa [Estrada-Cuzcano et al., 2012]</td>
</tr>
<tr>
<td><strong>BBS2 (BBS), 16q21</strong> [Kopec-Black et al., 1993; Katsanis et al., 2001; Nishimura et al., 2001]</td>
<td>8%</td>
<td>BBSome</td>
<td>c.472–2A&gt;G, Hutterites [Innes et al., 2010]; c.565C&gt;T (p.R189*), Tunisia [M’hamdi et al., 2014]; c.311A&gt;C (p.D104A) and c.1895G&gt;C, Ashkenazi Jews [Fedick et al., 2014]</td>
<td>Milder phenotype for BBS1 compared to BBS2 and BBS10 [Hjortshøj et al., 2010]; Better visual acuity and larger ERG amplitudes compared to patients with mutations in other BBS genes [Daniels et al., 2012]; Among patients with p.M390R mutation, homozygotes showed a relatively more severe ocular phenotype than compound heterozygotes [Castro-Sanchez et al., 2015]; Patients with missense mutations in BBS1 had a lower level of biochemical cardiovascular disease markers compared to patients with BBS10 and other BBS mutations [Fosythe et al., 2015]</td>
<td>Biallelic BBS2 mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benailly et al., 2005]; Nonsyndromic retinitis pigmentosa [Skeivich et al., 2015]</td>
</tr>
<tr>
<td><strong>BBS3 (ARL6, RP55), 3q11.2</strong> [Sheffield et al., 1994; Chiang et al., 2004; Fan et al., 2004]</td>
<td>0.4%</td>
<td>Small GTPase, participates in BBSome assembly</td>
<td>c.272T&gt;C (p.I91T), India [Sathya Priya et al., 2014]</td>
<td>Myopia was associated with BBS3 and BBS4, but not BBS2 mutations [Heon et al., 2005]</td>
<td>Nonsyndromic retinitis pigmentosa [Akdahmesh et al., 2009]</td>
</tr>
<tr>
<td><strong>BBS4, 15q22.32, q23</strong> [Carmi et al., 1995; Mykytyn et al., 2001]</td>
<td>2%</td>
<td>BBSome</td>
<td>c.77_220del144, Iran [Mykytyn et al., 2001]</td>
<td>Characteristic ocular phenotype (sparse amount of abnormal retinal pigment deposits even in advanced disease stage; amorphous appearance of the deposits) [Riise et al., 2002]; Myopia was associated with BBS3 and BBS4, but not BBS2 mutation [Heon et al., 2005]</td>
<td>Biallelic BBS4 mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benailly et al., 2005]</td>
</tr>
<tr>
<td><strong>BBS5, 2q31</strong> [Young et al., 1999; Li et al., 2004]</td>
<td>0.4%</td>
<td>BBSome</td>
<td></td>
<td></td>
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<tr>
<td><strong>BBS6 (MKS, MR5), 20p12</strong> [Katsanis et al., 2000; Slavotinek et al., 2000]</td>
<td>6%</td>
<td>Chaperonin complex</td>
<td>Patients with mutations in BBS6, BBS10 or BBS12 genes had more severe renal disease [Imhoff et al., 2011]</td>
<td>McKusick-Kaufman syndrome [Schafer et al., 2011]; Biallelic BBS6 mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benailly et al., 2005]</td>
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<tr>
<td><strong>BBS7 (FLJ10715, BBS2L1), 4q77</strong> [Badano et al., 2003b]</td>
<td>2%</td>
<td>BBSome</td>
<td>c.1967_1968delTAinsC (p.L656Pfs*18), Russia [Suspitsin et al., 2015]</td>
<td></td>
<td></td>
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<tr>
<td><strong>BBS8 (TTC8, RP51), 14q32.1</strong> [Ansley et al., 2003]</td>
<td>1%</td>
<td>BBSome</td>
<td>c.459+1G&gt;A, Tunisia [M’hamdi et al., 2014]</td>
<td></td>
<td>Nonsyndromic retinitis pigmentosa [Goyal et al., 2016]</td>
</tr>
<tr>
<td>Gene (synonym), chromosome localization</td>
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<tr>
<td>BBS9 (PTHBI, B1, D1, CI8), 7p14 [Nishimura et al., 2005]</td>
<td>6%</td>
<td>BBSome</td>
<td></td>
<td></td>
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<tr>
<td>BBS10 (C12orf58, FLJ23560), 12q21.2 [Stoetzel et al., 2006]</td>
<td>20%</td>
<td>Chaperonin complex</td>
<td>c.271_272insT (p.C91Lfs*5), people of European descent [Stoetzel et al., 2006; Muller et al., 2010; Billingsley et al., 2011]</td>
<td>Patients with BBS10 mutations had significantly higher BMI-Z, greater visceral adiposity, and greater insulin resistance than those with BBS1 mutations [Feuillan et al., 2011]; A higher frequency of urogenital anomalies in patients with BBS10 vs. BBS1 mutations was observed [Castro-Sanchez et al., 2015]; Patients with mutations in BBS6, BBS10 or BBS12 genes had more severe renal disease [Imhoff et al., 2011]</td>
<td></td>
</tr>
<tr>
<td>BBS11 (TRIM32, HT2A, LGMD2H, TATIP), 9q31q34.1 [Chiang et al., 2006]</td>
<td>0.1%</td>
<td>E3 ubiquitin ligase, involved in membrane trafficking</td>
<td></td>
<td></td>
<td>Limb-girdle muscular dystrophy type 2H, sarcotubular myopathy [Frosk et al., 2002]</td>
</tr>
<tr>
<td>BBS12 (C4orf24, FLJ35680), 4q27 [Stoetzel et al., 2007]</td>
<td>5%</td>
<td>Chaperonin complex</td>
<td>c.1156–1157CG&gt;TA (p.Arg386*), Iran [Fattahi et al., 2014]</td>
<td>A higher frequency of cognitive impairment in patients with BBS12 vs. BBS1 mutations was observed [Castro-Sanchez et al., 2015]; Patients with mutations in BBS6, BBS10 or BBS12 genes had more severe renal disease [Imhoff et al., 2011]</td>
<td></td>
</tr>
<tr>
<td>BBS13 (MKS1, FLJ20345), 17q23 [Leitch et al., 2008]</td>
<td>4.5%</td>
<td>Basal body, participates in organization of the transition zone</td>
<td></td>
<td></td>
<td>Meckel syndrome [Consugar et al., 2007]</td>
</tr>
<tr>
<td>BBS14 (CEP290, NPHP6, 3H11Ag, BBS4, CT87, IBTSS, LCA10, MKS4, POC3, SLSN6, rdl6), 12q21.3 [Leitch et al., 2008]</td>
<td>1%</td>
<td>Basal body, participates in organization of the transition zone and cilary entry of BBSome</td>
<td></td>
<td></td>
<td>Joubert syndrome, nephronophthisis, Senior-Loken syndrome, Meckel syndrome, Leber congenital amaurosis [Coppieters et al., 2010]</td>
</tr>
<tr>
<td>BBS15 (WDPCP, C2orf96, CHDTHP, FRTIZ, FR7TZ), 2p15 [Kim et al., 2010]</td>
<td>1%</td>
<td>Basal body, involved in regulation of septins localization and ciligenesis</td>
<td></td>
<td></td>
<td>Exome sequencing identified a compound heterozygous mutation in a young girl with polydactyly, coarctation of the aorta, and tongue hamartomas [Saaari et al., 2015]</td>
</tr>
<tr>
<td>BBS16 (SDCCAG8, NPHP10, CCCAP, CCCAP SLSN7, HSPC085, NY-CO-8, SLSN7, NCCACP), 1q43 [Otto et al., 2010; Billingsley et al., 2012]</td>
<td>1%</td>
<td>Basal body, regulates pericentriolar material recruitment to the centrosomal region</td>
<td></td>
<td></td>
<td>Absence of polydactyly [Schaefer et al., 2011]; Senior-Loken syndrome [Otto et al., 2010]</td>
</tr>
<tr>
<td>BBS17 (LZTFL1), 3p21.3 [Marion et al., 2012; Schaefer et al., 2014]</td>
<td>?</td>
<td>BBSome, participates in the Shh signaling</td>
<td></td>
<td></td>
<td>Mesoaxial polydactylyy [Schaefer et al., 2014]</td>
</tr>
<tr>
<td>BBS18 (BBIP1, BBIP10, bA348N5.3, NCRNA00081), 10q25.2 [Scheidecker et al., 2014]</td>
<td>?</td>
<td>BBSome</td>
<td></td>
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</tbody>
</table>
leaving the possibility that some of the accounted variants are actually benign. It is beyond any doubt, that at least a part of the observed phenotypic variability is not at all related to conventional genetic factors; for example, Beales et al. [1999] described monozygotic twins; one boy presented with polydactyly in 3 limbs, while his brother did not have additional fingers at all.

There is experimental evidence that some of the BBS mutations may render dominant-negative effect, e.g. by affecting the function of the remaining (wild-type) gene allele [Zaghloul et al., 2010]. The dominant-negative model may explain the increased incidence of heterozygous BBS gene mutation carriers in patients with BBS syndrome as well as the role of single-copy gene alterations in triallelic inheritance [Fauser et al., 2003; Hichri et al., 2005; Hjortshøj et al., 2010]. Some reports indicate an increased incidence of isolated BBS-related symptoms in parents of BBS patients and/or heterozygous carriers of the BBS gene mutations, while other studies disagree with this statement [Croft et al., 1995; Beales et al., 1999; Cox et al., 2003; Hjortshøj et al., 2007; Kim et al., 2007; Webb et al., 2009].

Table 1 (continued)

<table>
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</tr>
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<tbody>
<tr>
<td>BBS20 (IFT172, NPHP17, SRTD10SLB, win, RP71, orn-1), 2p23.3 [Bujakowska et al., 2015; Schaefer et al., 2016]</td>
<td>?</td>
<td>Involved in intraflagellar transport</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBS21 (?) (NPHP1, NPH1, JBT4, SLN1), 2q13 [Lindstrand et al., 2014]</td>
<td>?</td>
<td>Mediates anchoring of the basal body to the plasma membrane and assembly of the primary cilium</td>
<td>290-kb deletion, people of Northern European descent [Konrad et al., 1996]</td>
<td>One BBS patient described by Lindstrand et al. [2014] carried a homozygous NPHP1 deletion together with a homozygous benign variant in BBS2; BBS patients from another pedigree demonstrated a combination of a heterozygous deletion in NPHP1 and a heterozygous null mutation in BBS10</td>
<td>Nephromphosphia [Renkema et al., 2014]; Senior-Loken syndrome, Joubert syndrome [Hildebrandt et al., 2011]</td>
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</table>

* Forsythe and Beales [1993, 2013].
Experimental Therapeutics

Management of patients with BBS symptoms is largely restricted to symptomatic treatment and is unable to prevent the development of the most debilitating complication, i.e. blindness. Topical delivery of the missing BBS gene, e.g. by subretinal injection of BBS-containing adenovirus construct, rescued rhodopsin mislocalization and preserved the function of the eyes in experimental mice [Simons et al., 2011; Seo et al., 2013]. There were also some attempts to prevent apoptosis of photoreceptor cells by various pharmacological compounds [Mockel et al., 2012]. Administration of the melanocortin receptor agonist, melanotan II, attenuated obesity in BBS knockout mice, probably due to the activation of downstream leptin receptor signaling [Seo et al., 2009]. The inhibition of specific signaling molecules, such as mTOR by rapamycin or selected cyclin-dependent kinases by roscovitine, partially restored renal structure and function in zebrafish BBS models [Tobin and Beales, 2008]. There is an exceptionally interesting case report on a BBS-affected 21-month-old girl, who underwent comprehensive testing for biochemical deficiencies and was subsequently subjected to appropriate nutritional correction. Astonishingly, this child experienced a remarkable improvement of vision, resolution of obesity, normalization of behavior and mood, and restoration of normal development during the following 2 years and remained virtually healthy by the time of publication, i.e. being 7 years old [Genuis and Lobo, 2011]. While already established organ anomalies are notoriously difficult to treat, the mere delaying of BBS symptoms, if started from birth, may eventually turn out to be a feasible strategy.

Perspectives

The invention of next-generation sequencing offers an opportunity to discover new BBS loci and thus explain the missing heritability in BBS patients without mutations in BBS1–BB20 genes [Billingsley et al., 2011]. It has to be remembered that the most popular next-generation sequencing technology, whole-exome sequencing, is currently unable to reliably detect large gene rearrangements. Searching for gross alterations in already known and novel BBS genes currently requires different arrays of molecular tests, and they remain to be performed in BBS patients with unknown genetic causes of the disease. The existence of significant ethnic variations in the spectrum of affected genes calls for collection of patients and their genetic analysis in yet unstudied communities across the world. We are eagerly awaiting interventional trials in humans. Some of them, especially the ones based on gene therapy, may take years to come due to safety concerns as well as difficulties in organizing sophisticated gene-specific procedures for such a rare and heterogeneous multiorgan disease. Other approaches, e.g. as in the above-mentioned case based on nutritional correction [Genuis and Lobo, 2011], deserve rapid clinical assessment. In addition, population-based genetic screening is gradually becoming more achievable, thanks to decreasing costs and improving throughput for DNA-based assays. Routine identification of carriers of BBS mutations may eventually reduce the disease burden by revealing families at-risk and taking appropriate preventive actions [Genuis and Lobo, 2011; Baker et al., 2013].

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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Bardet-Biedl Syndrome

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Suspisin/Imyanitov


